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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,466	03/01/2004	Steven Louis Shafer	44893-0004	9229

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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	PAPER NUMBER
1616	

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03/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,466	SHAFER ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-39,41-43 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-39, 41-43, and 48* is/are rejected.

7)☒ Claim(s) *48* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 29-39, 41-43, and 48 are pending. Applicants previously cancelled claims 1-28, 40, and 47. Applicants have newly cancelled claims 44-46. Applicants have amended claims 37, 39, and 48. Receipt and consideration of Applicants' amended claim set, terminal disclaimer, and remarks/arguments submitted on December 3, 2008 are acknowledged. All rejections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments.

Moot Rejections/objections

All rejections and/or objections of claims 40 and 47 cited in the previous office action mailed on November 6, 2007 **are moot**, because said claims have been cancelled.

Claim Objections

Claim 48 is objected to because of the following informalities: the word "a" on line 1 of claim 48 should be changed to "the" to correctly refer to the method of claim 37. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention s not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29-39, 41-43, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mezei et al. (U.S. Patent No. 5,451,408) or Mezel et al. (RE38,407) in view of Dershwitz et al. ("Pharmacokinetics and pharmacodynamics of inhaled versus intravenous morphine in healthy volunteers," Anesthesiology, 2000, 93(3), pp 619-628 (Abstract Only)) and Shafer et al. ("Pharmacokinetics, Pharmacodynamics, and Rational Opioid Selection," 1991, 74(1), pp 53-63 (Abstract Only).

Applicant Claims

Applicants claim (1) a formulation comprising a rapid onset opioid selected from the group consisting of fentanyl, remifantanil, alfentanil, and sufentanil and a sustained effect opioid selected from morphine and methadone; (2) a pulmonary drug delivery device comprising (a) fentanyl and liposomally encapsulated fentanyl or (b) the combination of (i) remifantanil, alfentanil, sufentanil, or fentanyl and (ii) methadone; and (3) a method of administering an opioid to provide analgesia comprising (i) continuously administering an opioid formulation using a pulmonary drug delivery device and stopping inhalation when adequate analgesia is achieved, wherein the composition is as described in (2) above.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The disclosure of Mezei and Mezel are the same. The following citations to Mezei correspond to the same citations in Mezel, unless stated otherwise.

Mezei discloses **liposome-encapsulated opioid analgesic agents delivered by the pulmonary route** provide local or systemic analgesia superior to that produced by the solution form of these agents administered by parenteral (intravenous, intramuscular, or subcutaneous injection) or oral routes (abstract). The inhalation of liposome-encapsulated opioid analgesic agents offers the following benefits as a method of analgesic drug administration: (1) a simple and noninvasive route of administration; (2) a **rapid onset of analgesia** from absorption of free opioid (in **the range of 10-20% of the opioid dose**); (3) a **sustained analgesia** from continued release of liposome-encapsulated opioid (**approximately 80-90% of the opioid dose**) and (4) a low cost. The sustained release property of the liposomal product can be regulated by the nature

of the lipid membrane and by the inclusion of other excipients in the composition of the liposomal products (col. 3, lines 60-63; col. 4, lines 12-15, 18-27). Mezei's liposome-encapsulated opioid analgesic agents can be delivered by direct inhalation of an aerosol using any of the variety of known methods for delivering drugs through the pulmonary system. Representative active ingredients include **fentanyl, alfentanil, sufentanil and morphine** (col. 5, lines 45-50 and 64-66). Mezei exemplifies compositions comprising **fentanyl citrate, alfentanil HCl, sufentanil, and morphine** in Examples 1-8, wherein each example formulation is representative of a 100 ml sample. Example 2 discloses a composition comprising 60 mg of fentanyl citrate in 100 ml water (600 micrograms of total opioid/ml; 60-120 micrograms of free fentanyl; and 480-540 micrograms of liposomally encapsulated fentanyl).

Mezel claims a method of providing systemic analgesia by administering both a free and liposome encapsulated opioid analgesic by inhalation via a patient's pulmonary system, said opioid being selected from the group consisting of fentanyl, alfentanil, and sufentanil or a salt form thereof (claims 11-25).

Dershwitz teaches an AERx pulmonary drug delivery system for the inhalation administration of morphine results in pharmacokinetic data very similar to pharmacokinetic data due to the intravenous administration of morphine (Abstract) and concludes that the onset and duration of effects of morphine are similar after intravenous administration or inhalation via Dershwitz' pulmonary drug delivery device.

Shafter describes computer simulations of a pharmacokinetic-pharmacodyanmic model for an intravenous bolus or continuous infusion of fentanyl, alfentanil, and sufentanil, which are all well-known opioid analgesics. Shafer's model suggested that alfentanil was most suitable for

operations lasting 6-8 hrs and that sufentanil has a longer distribution and elimination half-lives than alfentanil (abstract).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Mezei/Mezel lack the express teaching of (1) continuous inhalation via a pulmonary drug delivery device, (2) administration is solely through the conscious effort of the user, (3) device mass of 250- 2,500 grams, (4) an outlet in the device through which the formulation is dispensed, and (5) the intended pharmacokinetic profile of the claimed formulation upon administration. These deficiencies are obvious per the teachings of Mezei/Mezel and/or are obviated per the teachings of Dershwitz and Shafer.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to an ordinary skilled artisan at the time of Applicants' claimed invention to modify the Mezei/Mezel composition to comprise a combination of two or more opioids, because opioids are art-recognized analgesic agents and the art recognizes that different opioids exhibit different pharmacodyanmic-pharmacokinetic profiles (Dershwitz and Shafer). Furthermore, it is noted that the claims of Mezel utilize open claim langauge and do not prohibit the inclusion of more than one kind of opioid analgesic and both Mezei and Mezel identify fentanyl, alfentanil, sufentanil and morphine as suitable opioids for inhalation administration. Regarding the continuous inhalation until sufficient analgesia is achieved, this would have been prima facie obvious because opioids are indicated for the treatment of pain (i.e. conveying analgesic effects) and as such would be administer in amounts

and frequencies needed for a given patient to obtain adequate pain relief. Furthermore, per the teachings of Shafer and Dershwitz, one would conclude that the pharmacokinetic-pharmacodyanmic (PK/PD) behavior of these opioids is well known. As a consequence the ordinary skilled artisan, using Dershwitz' pulmonary drug delivery device and Shafer's computer simulations, could reasonable predict the PK/PD profile of a particular combination of two or more known opioid analgesics. Thus, the combination of two opioids represents the optimization of the desired PK/PD profile to achieve suitable analgesia. Concerning the mass of the drug delivery device, it is common sense that one would optimize an inhalation drug delivery device to not be excessively heavy and thus facilitate its use by patients of varying ages and overall health, who would reasonably be expected to exhibit varying capacity to hold an inhalation device. Concerning the device having an outlet it is common sense that for an inhalation device to work properly and be suitable it would have to have an outlet from which drug could be dispensed. In fact, it is conventional for inhalation devices (e.g. inhalers) to comprise outlets from which aerosolized formulations are delivered to a patient for inhalation. An ordinary skilled artisan would have had a reasonable expectation of successfully formulating a composition comprising two or more different opioid analgesics, because opioid analgesics are well known in the art. Similarly, given that PK/PD profiles of commonly available and well-known opioid analgesics are known (Dershwitz and Shafer); computer simulations predictive of said PK/PD profiles for opioid analgesics are known; inhalation drug delivery devices are known; and inhalation administration of opioids results in similar PK/PD profiles as intravenous administration of opioid analgesics (Dershwitz) an ordinary skilled artisan would have had a reasonable expectation of success in continuously administering the Mezei/Mezel formulations

until sufficient analgesia was obtained. Regarding the relative amount of the two opioids, the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 12/3/08 have been fully considered but they are not persuasive. Applicants allege that the instant rejection is improper, especially because (1) the rejection does not explicitly indicate why inhalation as a result of the conscious effort of the user is obvious and typically opioids are administered to pain suffers by physicians or other health professionals; (2) the claimed method is allegedly unobvious because the user can be responsible for their own medication and can discontinue administration once adequate analgesia has been achieved; and (3) the claimed method is allegedly distinct because it does not require the use of instrumentation to intervene or control the user's intake of medicine.

The Examiner respectfully disagrees with Applicants' traversal arguments. Regarding (1), although it is conceded that the prior art does not explicitly state that inhalation would occur through the conscious effort of the user, this aspect is impliedly present in the prior art teachings. Inhalation is usually a natural process that occurs absent conscious effort and so long as an individual remains alive and in normal health, is always followed by exhalation. Inhalers are well-known in the art and it is common sense that a patient's use of an inhaler requires the patient's conscious effort, because unconscious individuals are not capable of using inhalers and patients routinely self-administer pharmaceutical formulations via their conscious efforts by utilizing inhalation devices. Thus, the fact that the prior art does not explicitly teach the requirement that a patient will administer a therapeutically effective dose of an opiate by inhalation through their conscious effort is not missing from the prior art.

Regarding (2), opioid agonists are well known analgesics for the treatment of pain as set forth above. Furthermore, the concept of having a patient self-administer a dose of an opioid until adequate analgesia results is well-known. For example, Stanley (U.S. Patent No. 5,288,498) taught the dose-to-effect dosing of opiates by patients in 1994 (see col. 8, lines 18-23; col. 20, lines 48-51; col. 21, lines 1-13[Table 1]; claims 1 and 101). Stanley has been provided herein only to address Applicants' arguments. Furthermore, it is clear that a patient self-administering an opioid could stop administration once adequate analgesia was obtained. Thus, having a patient dose-to-effect an opioid agonist (e.g. fentanyl) using an inhaler is obvious.

Regarding (3), Applicants' claimed method necessarily requires instrumentation to intervene with a user's intake, because Applicants' method requires the administration of a drug formulation utilizing a pulmonary drug delivery device. To intervene can mean to come between

as in space and time. Thus, Applicants' method requires the intervention of a pulmonary drug delivery device (i.e. the device is physically between the inhaler and the pharmaceutical composition and mediates the pulmonary administration). Thus, the prior art teaching that opioid formulations can be administered by aerosol inhalation, which necessarily requires the intervention of a pulmonary drug delivery device, requires the same instrument intervention as Applicants' claimed method.

Regarding the PK/PD limitations recited in Applicants' claim 48, it is noted that Mezei/Mezel's Figure 1 depicts PK/PD data for the administration of the invented fentanyl/liposomally encapsulated fentanyl formulations. It is the Examiner's position that the duration of the peak plasma concentration could be controlled by the ordinary skilled artisan by optimization of the ratio of the fentanyl to liposomally encapsulated fentanyl or another rapid effect/slow effect opioid combination. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 37-39, 41-43, and 48 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 10-25 of U.S. Patent No. RE38,407 (RE'407) in view of Dershwitz et al. ("Pharmacokinetics and pharmacodynamics of inhaled versus intravenous morphine in healthy volunteers," Anesthesiology, 2000, 93(3), pp 619-628 (Abstract Only)). Although the conflicting claims are not identical, they are not patentably distinct from each other because both claim sets claim methods and formulations comprising opioid analgesics, such as a combination of a free opioid and a liposomally encapsulated opioid, for providing analgesia to a patient in need thereof. The cited claims of RE'407 do not recite a pulmonary drug delivery device. This limitation is cured by the teachings of Dershwitz set forth above. The claims of RE'407 do not explicitly recite the combination of two or more different opioids in a single formulation. This limitation is obvious, because opioid analgesics are known to have the same utility in the prior art (i.e. analgesia). It is generally considered *prima facie* obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. See *In re Kerkhoven*, 626, F.2d 848, 205 USPQ 1069 (CCPA 1980). As shown by the recited teachings, the instant claims define nothing more than the concomitant use of two known opioid analgesic agents. It would follow that the recited claims define *prima*

facie obvious subject matter. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 37-39, 41-45, and 48 *prima facie* obvious over claims 1 and 10-25 of U.S. Patent No. RE38,407 (RE'407) in view of Dershwitz et al. ("Pharmacokinetics and pharmacodynamics of inhaled versus intravenous morphine in healthy volunteers," Anesthesiology, 2000, 93(3), pp 619-628 (Abstract Only)).

Response to Arguments

Applicant's arguments filed 12/3/08 have been fully considered but they are not persuasive. Applicants' traversal arguments are the same arguments rebutted above with respect to the rejection under §103(a). The rebuttal arguments presented above are herein incorporated by reference.

Conclusion

Claims 29-39, 41-43, and 48 are rejected. Claim 48 is objected. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571)

272-5548. The examiner is on a flexible schedule, but can normally be reached M-F ~10 am ~5:30 pm, and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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